Australia

Patents Act 1990

IN THE MATTER OF Australian Patent Application Serial No. 696764 by Human Genome Sciences, Inc

and

IN THE MATTER OF Opposition thereto by Ludwig Institute for Cancer Research.

STATUTORY DECLARATION

I, Francis John Ballard, of 21 Willowbridge Grove, Burnside, South Australia, 5066, do solemnly and sincerely declare as follows:

INTRODUCTION

1.1 Ludwig Institute for Cancer Research ("Ludwig Institute") has asked for my services as a scientific expert in connection with Ludwig Institute's opposition to the issuance of an Australian patent to Human Genome Sciences, Inc., ("HGS") based on HGS's Australian Patent Application No. 696764. The patent application relates generally to an isolated polynucleotide and protein for an alleged novel vascular endothelial growth factor called "Vascular Endothelial Growth Factor 2" ("VEGF2").

1.2 The first evidence that I provided in the opposition proceeding was a declaration from February 2000 (hereinafter referred to as "OJB1" (Opponent, John Ballard, 1st Declaration)). My first declaration included a brief resume of my scientific experience, and explained that I had reviewed and agreed with a detailed declaration executed by Peter Rogers (hereinafter "OPR1"), which I will refer to again in this declaration.

1.3 In response to Ludwig Institute's initial evidentiary submission, HGS filed declarations from six scientists, John Stanley Mattick (hereinafter "AJM1"(Applicant, John Mattick, 1st Declaration)), Jennifer Ruth Gamble ("AJG1"), Nicholas Kim Hayward ("ANH1"), Thomas Rapoport ("ATR1"), Stuart Aaronson ("ASA1"), and Susan Power ("ASP1").

1.4 In this declaration I respond to issues raised by the HGS declarants. Ludwig Institute asked me to give special emphasis to issues involving protein expression, which is one of my areas of scientific expertise. Failure to address any specific issues raised by any of the HGS declarants should not be interpreted as agreement with any HGS declarant. For the purpose of preparing this declaration I have reviewed the HGS declarations, first and second declarations made by Professor Alitalo (OKA1 and OKA2) and first and second declarations made by Professor Rogers (ORP1 and OPR2).

1.5 I hereby reaffirm my understanding that I have an overriding duty to the Patent Office (and to any Australian Federal Court that should review the Patent Office decision) to provide objective scientific analysis that I believe to be truthful. I hereby affirm that, to the best of my knowledge and belief, factual statements herein are true and opinion statements herein represent my objective scientific opinion and analysis.

1.6 Unless I specifically state otherwise below, I affirm the facts and opinions expressed in my prior declaration (i.e., in OJB1). Nothing in HGS's evidence-in-answer causes me to change the opinions embodied in my first declaration.

GENERAL COMMENTS ON THE EVIDENCE IN ANSWER

2.1 The HGS declarants that reviewed Professor Alitalo's declaration (filed as part of Ludwig Institute's evidence-in-support) criticised the conclusions of Professor Alitalo's declaration [See AJG1 at 7.43 and 7.52; ANH1 at 5.6-5.13; and ASA1 at 11, 13, 14, and 18]. The Alitalo declaration provided clear specific evidence that VEGF2 cannot be expressed and secreted in the manner taught in the opposed application. In my opinion, the criticisms made of Professor Alitalo's experiments

and conclusions are without merit, and are not consistent with the approach taken by the HGS declarants in the evidence in answer.

2.2 The HGS declarants accept, without analysis, that VEGF2 can be expressed as suggested in the opposed application.[1] However, the opposed application does not provide any experimental evidence of expression of VEGF2 in a cell. This fact is especially ironic because, when the HGS declarants discuss how they would have tried to express VEGF2, they have clearly abandoned the teachings of the application in favour of alternative ideas. (See discussion below.)

2.3 The HGS declarants also suggest that VEGF2 has a particular biological activity (OPR1 at 2.3.2, 2.7.4, 3.4.2, 4.6, 4.6.1-4.6.5, 4.8, 5.4, 5.5, and 5.9.). However, I note that the opposed application does not provide evidence of biological activity, and none of the declarants have described any additional experiments to demonstrate biological activity[2]. Additionally the opposed application contains no evidence that VEGF2 can be used for therapeutic purposes, contrary to the suggestions made by the HGS declarants (OPR1 at 2.3.3-2.3.4, 3.7.1, 4.6.3, and 6.8.1-6.8.4.)

2.4 In my opinion, the evidence of Professor Alitalo in his first and second declarations, and the evidence of Dr Power (which is not based on the opposed application) demonstrates that the VEGF2 invention does not work as it was described in the opposed application, because it is incomplete.

2.5 A further example of this lack of analysis on the part of the HGS declarants is seen in the declaration of Dr Gamble. Dr Gamble acknowledges the existence of Professor Alitalo's experimental results, but says, without foundation, "In my opinion Professor Alitalo's conclusions represent pure speculation and cannot reasonably be drawn from the results presented in his statutory declaration . . . ."

---

1 See, e.g., AJM1 at 4.19-4.23 (uses for VEGF2 alleged in the application) and 4.24 (in which Dr Mattick concludes that these unsupported uses "constitutes the basic information that I would have required in 1994 to use VEGF-2 in a wide range of biological activities.") [See AJM1 at 3.31, 3.33, 4.3-4.13, 4.77-4.78; AJG1 at 6.5, 6.8, 6.11, 7.24, 7.46, 7.48; ANH1 at 3.15, 3.19-3.23, 3.26, 4.20; ATR1 at 9-12; and ASA1 at 6 and 17]

2 To the extent that HGS has pointed to evidence of activity in the literature, such literature relates to molecules other than VEGF2 of the opposed application.

2.6 By contrast, Dr. Gamble's declaration itself does not identify any experimental evidence that supports the teachings of the opposed application in relation to the properties of the VEGF2 sequence there defined. Again without evidence, Dr. Gamble says, "in my opinion, the patent specification fully enables one to express and secrete a biologically active protein that has been correctly processed."[3] (AJG1 7.24.) In my opinion, that suggestion should simply be discounted as "pure speculation" because it lacks any foundation. Viewed objectively, Professor Alitalo has provided the only actual evidence in this proceeding about whether VEGF2 of the opposed application is expressed and secreted by cells, and he finds that it is not.

2.7 In the context of the relevance of the prior art, the conclusions drawn by the HGS declarants cannot be supported. For example, I note that Dr. Mattick indicates that no conclusions can be drawn about whether antibodies raised against a prior art VEGF polypeptide will cross react with *identical* sequences that occur in VEGF2 on a theoretical level because to draw such conclusions he would require actual experimental data. (AJM1 4.33) However, this position is inconsistent with his subsequent statement that "computer programs were *readily available* in 1994 to generate" information about "all of the antigenic sites on the VEGF-2 molecule." (AJM1 4.83)

2.8 These and other examples discussed below indicate a lack of thorough and objective scientific analysis in the HGS declarations.

LACK OF FAIR BASIS AND INSUFFICIENCY

3.1 Sections 4 and 5 of OPR1 explained that the opposed application described an incomplete and non-working invention. More specifically, that the description of the invention was not adequate to practice the invention as claimed. I agree with those statements. In my opinion, the claims made by HGS in the opposed application are not based upon the invention described in the opposed application.

---

[3] Dr. Gamble says the total absence of working examples to be "largely irrelevant." (AJG 7.18)

Indeed, as I and Professor Rogers have previously stated, "VEGF2" as taught in the opposed application is incomplete and could not be expressed and secreted as a protein, and there is simply no experimental evidence that "VEGF2" as taught has any of the activity alleged in the application. Even if one or a few of the activities that were alleged should prove to be legitimate, they are buried in a list of activities and alleged uses that would have taken considerable time and effort to test. HGS's contribution is limited (sequencing of an (incomplete) cDNA, doing a database sequence comparison, and doing a Northern blot mRNA expression study) and did not provide sufficient information to predict structure or function of the VEGF2 protein alleged as the invention. In no way does it reflect the amount of experimentation needed to make the invention work.

3.2 In fact, as also noted by Professor Rogers in OPR1, the protein that the human body produces *in real life* from the VEGF2 gene has a structure that is substantially different to that taught by HGS in the opposed application. The protein's principal function in adult tissues appears to be in regulation of the lymphatic system. That function was not described or suggested in the HGS application, but was instead determined by Alitalo *et al.* I agree with Professor Rogers in OPR1 that many of the HGS claims were not based on the application as it was filed, but rather, were an attempt to capture inventions such as those of Alitalo *et al.* that were published during the pendency of the opposed application before the Patent Office, but that owed nothing to the contributions embodied in the opposed application.

A. The Use of "VEGF2" Versus "VEGF-C" Nomenclature

3.3 Throughout the evidence-in-answer, the HGS scientists either state or suggest that "VEGF2" of the opposed application is the same as "VEGF-C," as described by Professor Alitalo and his colleagues in a number of articles and patent documents. For instance, Dr. Mattick explains that "HGS' Patent Attorneys have informed me that VEGF-2 and VEGF-C are the same molecule." (AJM1 at 3.3.) Dr. Gamble says "Today, VEGF-2 is identified by the nomenclature VEGF-C. When I read VEGF-2 in the patent specification I understand it to mean VEGF-C" (AJG1 at 3.1.) Dr. Rapoport says, "It is my

understanding that VEGF-2 and VEGF-C are terms used to refer to the same molecule." (ATR1 at 13.) Dr. Rapoport uses the two terms interchangeably. (ATR1 at 13.).

3.4 It may be true that VEGF2 and VEGF-C proteins share a high level of amino acid sequence identity since both were derived from the same human gene. However, this nomenclature was given by two independent research groups within the context of their individual laboratory experiments. These groups taught very different things about their work, as set out in detail below. Any suggestion that these two names represent the same molecule (and the implication that the properties of VEGF-C are attributable to VEGF2) ignores substantial differences which exist between them. For instance, the growth factor "VEGF-C" has been described in patent and scientific literature by Alitalo *et al.*,[4] and has been shown to have biological activity towards receptors, and to influence growth of the lymphatic system. The incomplete "VEGF2" sequence taught in the opposed application is apparently never expressed and secreted (see OKA1 and OKA2) and the scientific literature has no report of significant biological activity. Because VEGF-C described in the literature is a different molecule from VEGF2 in the opposed application, any reference to VEGF-C properties or reliance on VEGF-C literature by HGS (with regard to VEGF2 patentability issues) is inaccurate, incorrect and unfair.

3.5 Dr. Hayward also applies his knowledge of VEGF-C to support teachings in the opposed application relating to VEGF2. In ANH1, Dr. Hayward said, "I am aware that VEGF-2 is proteolytically processed upon secretion from cells in vivo to form the naturally occurring ligand for the Flt-4 and the KDR/Flk-1 receptors. I would expect a fusion of the 350 amino acid sequence of VEGF-2 to a signal sequence to be proteolytically processed to produce functional VEGF-2." (ANH1 at 3.22. See also ANH1 at 3.30-3.35) Dr. Hayward's comments represent another instance where an HGS declarant is incorrectly attributing VEGF-C properties to the VEGF2 polypeptide taught in the opposed application. The 350 amino acid VEGF2 as taught in the original

---

[4] See, e.g., OPR1 at 1.5.3-1.5.4 and Documents D71-D74.

application was not taught to be a ligand for any receptor, cannot be expressed and secreted by cells, and has never been reported in the literature to be a ligand for these receptors.

3.6 Figure 1, attached to this declaration as **Exhibit FBJ-1**, illustrates the substantial differences between the VEGF2 processing taught by HGS in the opposed VEGF2 application and VEGF-C processing taught by Professor Alitalo's research group. Column A on the left side of the figure depicts the process by which the literature had taught that the VEGF gene is transcribed into RNA, which is then translated into VEGF polypeptides having signal peptides, which are processed into mature VEGF polypeptides via removal of the signal peptide. Column C on the right side depicts processing of VEGF2 taught in the opposed application, which was apparently predicted from knowledge of VEGF, and follows a similar pattern of transcription, translation, and removal of a short signal peptide.

3.7 Column B of Figure 1 (**Exhibit FBJ-1**) depicts VEGF-C processing as determined experimentally by Professor Alitalo's research group. VEGF-C is originally translated as a 419 amino acid prepro-protein, not a 350 amino acid protein as taught in the opposed application for VEGF2. Not only is a signal peptide removed, but substantial additional processing also occurs in multiple steps at both ends of this prepro-VEGF-C protein. Professor Alitalo's group demonstrated that a heavily processed form of VEGF-C (lacking about 102 amino acids from the beginning (N-terminus) and about 190 amino acids from the end (C-terminus)) binds and stimulates the Flt4 and KDR/Flk-1 receptors. (See, e.g., Documents D70-71, D73, and D75.) In contrast, the opposed application fails to teach that VEGF2 is a ligand for any receptor or that VEGF2 is processed in that manner. Thus, when Dr. Hayward discusses what he expects in terms of VEGF2 proteolytic processing and receptor binding, he is apparently referring to published evidence generated by Professor Alitalo for VEGF-C, and not VEGF2 taught in the opposed application. His use of the term "VEGF2" when describing the work of Professor Alitalo suggests, improperly, that Professor Alitalo's work supports the opposed application. The molecule that has been shown to stimulate the Flt4 and KDR/Flk-1

receptors is the approximately 21kD mature VEGF-C at the bottom of Figure 1, column B, not the VEGF2 of the opposed application.

3.8 Column A of Figure 1 (**Exhibit FBJ-1**) is included because Dr. Gamble devotes several pages of her declaration to a discussion of prior art growth factors (PDGFs, VEGF, and PlGF), including the proteolytic processing of these proteins. (See AJG1 5.1-5.13.). Similarly, Dr. Rapoport's declaration also relies heavily on the analogy of VEGF and PDGFs processing for his declaration. (*See, e.g.*, ATR1 at 7, 9, and 11.).

3.9 The HGS declarants state they would predict similar VEGF2 attributes based upon the prior art (e.g., based on VEGF prior art). (See AJG1 6.5: "Thus, I would predict that VEGF-2 would be expressed in a similar way." See also AJG1 6.10 - 6.11; ANH1 at 3.15; ATR1 at 11: "I would predict VEGF-2 to be expressed in a similar way [as the PDGF/VEGF family of growth factors].") HGS made exactly the type of prediction in the opposed application, when HGS predicted that VEGF2 processing consists of a simple removal of a signal peptide, similar to what was known for VEGF. (Compare Figure 1, columns A and C (**Exhibit FBJ-1**)). As shown by Professor Alitalo and explained above, HGS's inventors were incorrect with their predictions of the correct signal peptide and mature protein sequences. So, too, would the HGS declarants have been wrong in predicting VEGF2 expression and processing based on the prior art. Amino acids 1-24 of VEGF2 do not function as a signal peptide (see OKA1 and OKA2). The full length 419 amino acid protein (VEGF-C) is processed in an unexpectedly different and more complex manner, compared to simple removal of a signal peptide. (See Figure 1, column B; OPR1 at 4.11.1.3; and Documents D70, D71, D73, and D74 cited therein.) Therefore, I disagree with Dr. Gamble's suggestion that "VEGF-2 is no different in that it contains a signal or leader sequence." (See AJG1 at 6.4; see also AJG1 at 6.3) Rather, the processing of the full length VEGF-C protein is considerably different. Even when HGS filed its second patent

application, they still badly mis-predicted the manner in which the protein is processed.[5]

3.10 Professor Alitalo has shown that the incomplete VEGF2 taught in the opposed application is not expressed and secreted at all, e.g., that HGS's prediction regarding proteolytic processing (See Figure 1 hereto (**Exhibit FBJ-1**), column c: VEGF2 of 350 amino acids; removal of signal peptide of 24 amino acids, producing mature protein of 326 amino acids) does not occur.

3.11 As I noted above, Professor Alitalo has conducted further experiments which were designed to address the criticisms made of the experiments that he discussed and analysed in his first declaration OKA1. In my opinion, the criticisms made of Professor Alitalo's first declaration OKA1 lacked validity. However, in any event, the experiments designed and conducted by Professor Alitalo and recorded in his second declaration OKA2 provide direct experimental evidence that cells cannot express and secrete VEGF2 as taught in the patent application. (See Professor Alitalo's declarations, OKA1 and OKA2.) The experiments include appropriate controls and are not refuted by any experiments provided by HGS. The application teaches that the approximately 350 amino acid VEGF2 comprises a leader (signal) sequence of approximately 24 amino acids that would direct secretion of a mature VEGF2 of about 326 amino acids. (See Figure 1, column C) In my opinion, Professor Alitalo's experiments were correctly designed to see if the encoding cDNA could be expressed and secreted as taught in the opposed application.

3.12 Professor Alitalo's experimental results, described in his first and second declarations, demonstrate that VEGF2 is not expressed and secreted as taught in the opposed application. A number of the HGS declarants suggested that Professor Alitalo's scientific methods lacked suitable controls or were otherwise so defective that no conclusions could fairly be drawn from his

---

[5] In its later VEGF2 patent applications, HGS taught that the leader sequence of the 419 residue VEGF2 is approximately 23 residues, resulting in a mature protein of 396 residues (See Documents D43; and D44 at p. 7, last paragraph). As Figure 1 (**Exhibit FJB-1**) shows, the leader sequence is actually 31 amino acids, and additional processing results in a much smaller mature protein (see also Document D71).

experiments. (The declarants failed to provide any evidence of their own that VEGF2 is expressed and secreted as described in the application, and the application provides no evidence either.) In my opinion, the experiments described in OKA1 provided clear evidence that VEGF2 cannot be expressed and secreted as described in the opposed application. Subsequently, Professor Alitalo carried out a second series of experiments (described in OKA2). Those experiments again prove that VEGF2 can not be expressed and secreted as taught in the opposed application. In my opinion, the experiments described in OKA2 addressed all of the criticisms made by the HGS declarants of Professor Alitalo's original experimental results with regard to the choice of cell lines and antibodies. In my opinion, the results of Professor Alitalo's second experiments confirm the results of OKA1 and show that VEGF2 as taught in the opposed application can not be expressed and secreted from cells.

3.13 Knowing what we know today about VEGF2, at least a partial explanation for the lack of expression and secretion of VEGF2 is that the construct in the opposed application lacks a working signal peptide. Indeed, the opposed application teaches a signal peptide which is incorrect and non-functional. Specifically, the opposed application taught an incomplete VEGF2 sequence missing about 69 codons/amino acids at the beginning of the molecule, including the signal peptide. HGS's declarants have admitted this important omission from the patent application. (See Section 3 below.) When HGS discovered the missing 69 codons, HGS filed a second series of patent applications. (See, e.g., Document D43- D46.) Even when HGS determined that VEGF2 in the opposed application was incomplete, and filed the second patent application on the 419 amino acid VEGF2 more than a year later, HGS still failed to teach that VEGF2 was a ligand for Flt4 or any other receptor, and failed to teach the VEGF-C processing that was independently elucidated by Professor Alitalo's group.

3.14 Essentially, the only sections of the HGS declarations that relate to proteolytic processing that are relevant, are those admissions stating that the opposed application had erroneously identified the complete sequence. For example, Dr. Gamble plainly agrees that the VEGF2 signal/leader sequence "is located

among the 69 amino acids that were not disclosed in the patent specification." (AJG1 6.4 (emphasis added).)

3.15 In so far as any of the HGS declarants believed that publications relating to VEGF-C are relevant to patentability issues for the *incomplete VEGF2* taught in the opposed application, they are simply wrong. Professor Alitalo's experiments, embodied in his two declarations, demonstrate that the incomplete VEGF2 taught in the opposed application cannot be expressed and secreted. Mature VEGF-C, which can be expressed in a number of ways, is not taught in the opposed application.

3.16 Another example of HGS attempting to support the VEGF2 application by pointing to VEGF-C relates to VEGF-C patents. Dr. Mattick, Dr. Gamble, Dr. Hayward and Dr. Rapoport all make reference to U.S. Patent No. 6,130,071 (Alitalo *et al.*) to support their position that VEGF2 could be produced using the experimental approaches outlined in their declarations. (See AJM1 4.12; AJG1 6.5; ANH1 4.20; and ATR1 at 13)[6] In my opinion, the existence of the Alitalo patent indicates that all of the work that Professor Alitalo's group conducted merited a patent for Professor Alitalo. It was not routine work that should be credited to the opposed application of HGS. The "References Cited" portion of U.S. 6,130,071 patent cites Documents D43, U.S. Patent Nos. 5,932,540, 5,935,820 **(Documents D92 and Exhibit PAWR-11 of OPR2**, respectively), and International Application No. WO 95/24473 **(Exhibit PAWR-12 of OPR2)**, all of which appear to be related to the opposed application, in particular WO 95/24473 appears to be identical to the opposed application. I understand that inclusion of these documents in the "References Cited" section, indicates that each was considered by the U.S. examiner prior to issuing U.S. 6,130,071. The fact that the U.S. examiner believed the invention of 6,130,071, filed in 1997, to be patentable after considering the contents of the opposed application (through consideration of the aforementioned documents), indicates to me that the work described in the 6,130,071 patent is the inventive work of others, and owes little or nothing to

the opposed application's teaching. That is, it seems unlikely to me that the patented work of others merely reflects the efforts of routine experimentation.

3.17 Furthermore, I cannot see how the content of U.S Patent No. 6,130,071 could be said to support the opposed application. Contrary to Dr Gamble's representation (AJG1 at 6.5) the biologically active VEGF-C forms described in US 6,130,071 are not the 350 or 326 amino acid forms of VEGF2 as taught in the opposed application. In addition, the VEGF-C activities such as Flt4 receptor stimulation or lymphatic endothelial cell growth factor described in the Alitalo patent are not attributable to the opposed application. Professor Alitalo's research group had identified the full length 419 amino acid prepro-VEGF-C and had characterised the biological activities of mature VEGF-C at the time that they filed their 1997 patent application. It is unfair to suggest that this work should be credited to the opposed application, which taught an incomplete protein that is not expressed and secreted by cells and that has never been reported in the literature to have any activity.

3.18 Dr. Hayward also falsely attributes the teachings of Alitalo *et al.* to the inventors of the opposed application by declaring:

> "page 4 lines 12 to 14 of the patent specification states that the VEGF-2 polypeptides of the invention may be used to isolate receptors of VEGF-2. At page 24 fifth paragraph to page 25 first paragraph the patent specification discloses that VEGF-2 binds to tyrosine kinase receptors on the surface of target cells to activate endothelial cell growth." (ANH1 at 3.30.)

The opposed application speculates that VEGF2 receptors may exist but contains no teaching whatsoever of their identity. Even when HGS later filed its patent applications on the 419 amino acid VEGF2, they still did not describe the identity of any VEGF2 receptor. (See **Documents D44-D46**.)

---

[6] In paragraphs 13-15 Dr. Rapoport also relies on VEGF-C journal articles published by

B. The VEGF2 Invention Does Not Work

3.19 The evidence in answer shows a recognition by HGS's experts that the opposed application was completely wrong about VEGF2. They admit that the true VEGF2 signal peptide is missing, and then propose alternative ways of expressing VEGF2. However, the alternatives are NOT taught in the application.

3.20 For instance, Dr. Mattick admits "the fact that the signal sequence information was incomplete" (paragraph 4.13). His explanation of how he may have expressed VEGF2 begins with the presumption that an attempt to express the VEGF2 protein using the putative secretion signal sequence identified in the patent specification would not work. (See AJM1 4.5, and ensuing discussion in paragraphs 4.6-4.13; see also AJM1 4.76-4.78.) Ignoring those teachings, Dr. Mattick then explains how he would have deduced from the opposed application to express an approximately 373 amino acid VEGF2 sequence using a heterologous signal peptide (AJM1 4.7-4.8). Dr. Mattick admits, in the paragraph immediately following, that the application teaches only to attach a heterologous signal to "the mature sequence." (AJM1 4.9) Thus, the approach he is advocating for expressing VEGF2 is not an approach taught in the patent application.

3.21 In fact, Dr. Mattick's 373 amino acid construct is not described in the application at all. The application only describes an approximately 350 amino acid full length VEGF2 and mature VEGF2 of 326 amino acids. In essence, Dr. Mattick is saying that, after determining that the invention described in the patent application does not work, he may have been in a position to design some experiments to make something that is not described in the application, but in his opinion could work. However, he does not indicate that he has actually performed these experiments.

Professor Alitalo.

3.22 Dr. Gamble also admits that the VEGF2 invention is incomplete: "I note that a portion of the full length VEGF-2 sequence, which is not disclosed in the patent specification, is part of the NH2 (amino) terminal end of the full length polypeptide sequence. This equates to 69 amino acids . . . . [The VEGF-2 signal] sequence is located among the 69 amino acids that were not disclosed in the patent specification." (AJG1 at 6.4.) Of course, the patent application does not teach that anything is missing -- the missing sequence was discovered later. Nonetheless, Dr. Gamble proceeds as if she would have had knowledge of this defect in the patent application, and explains that "The mere fact that the sequence disclosed in the patent application does not include the first 69 amino acids of the full-length VEGF-2 sequence would not dissuade me from attempting to express the sequence disclosed in the patent specification with a heterologous signal sequence." (AJG1 at 6.5.) Thus, Dr. Gamble suggests she would have tried to attach a heterologous signal sequence to the approximately 350 amino acids of VEGF2 disclosed in the patent application. Dr. Hayward states that he would have used a similar approach. (See ANH1 at 4.20.) This approach is different than the one suggested by Dr. Mattick. It is not an approach taught in the opposed application.

3.23 Dr. Rapoport's explanation of the incomplete invention problem is similar. He is of the opinion that all secreted proteins have recognisable signal sequences (ATR1 at 4-6), but that no such sequence is seen in the VEGF2 of the application. (ATR1 at 10.) Faced with that evidence, however, he says he would not conclude that VEGF2 is not secreted, but rather that he would have had great confidence that VEGF2 was secreted, and would therefore have attached a "strong" foreign signal sequence to 350 amino acid VEGF2. (ATR1 at 12.) In his opinion "this approach is specifically taught in the HGS patent specification" at page 14. I disagree. The opposed application says nothing that can fairly be read as instructing attachment of a heterologous signal sequence to the portion of VEGF2 that was identified in the application as a signal sequence. This would, in effect, provide two signal sequences in tandem. I simply cannot see the sense in signal peptide redundancy in terms of recombinantly expressing polypeptides.

3.24 The experiments suggested by HGS's declarants are neither taught or suggested by the opposed application. The HGS declarants have devised them using information published after the opposed application was filed. Such information includes the knowledge that VEGF2 as taught in the opposed application is incomplete and cannot be expressed and secreted as taught in the application. Drs. Mattick, Gamble, Hayward, and Rapoport do not attempt to reproduce the invention described in the opposed application. Instead, they apparently read the application as one that teaches that mature VEGF2 is 326 amino acids, but would nevertheless have made a construct comprising a foreign signal peptide attached to VEGF2 of 350 or 373 amino acids. I cannot see why results of experiments not described in the opposed application should have any bearing on the adequacy of the application's teachings. To put it simply, these experiments are not disclosed nor suggested in the opposed application. By contrast, Professor Alitalo's experiments were based on the actual teachings in the application, and he showed that cells cannot express and secrete VEGF2 as taught in the application. In fact, the HGS declarants essentially abandon the direct teachings of the application and offer other methods for trying to express VEGF2. As such, they implicitly accept the experimental results of Professor Alitalo.

C. Dr. Power's Experiments

4.1 The teachings in the opposed application relating to full length and mature VEGF2 are clear: "The polynucleotide of the invention . . . contains an open reading frame encoding a protein of about 350 amino acid residues of which approximately the first 24 amino acid residues are likely to be leader sequence such that the mature protein comprises 326 amino acids . . . ." (page 5 last paragraph). Regardless of these unequivocal teachings, HGS has directed a substantial part of its declarations to discussing totally different VEGF2 proteins that were not taught in the application. (This is evident from the discussion in the preceding section.)

4.2 To provide another example, HGS asked Dr. Power to treat the 350 amino acid VEGF2 as "mature VEGF2" and express it via a different signal sequence:

"The Patent Attorneys for Human Genome Sciences (HGS) requested that I perform the following experiments in order to determine whether the 350 amino acid form of VEGF-2 (corresponding to residues 70 to 419 of the 419 amino acid form of VEGF-2) fused in frame with a heterologous signal sequence would result in the expression and secretion of the protein from eukaryotic cells." (ASP1 at 2.)

4.3 Dr. Aaronson cited with approval Dr. Powers work expressing a 350 amino acid VEGF2 with a different signal sequence. (See ASA1 at 15 - 22.)[7] Dr. Gamble also considers this approach for "attempting to express" the VEGF2 sequence which, with hindsight, she notes was missing the real VEGF2 signal sequence. (AJG1 6.4-6.5.)

4.4 These experiments may be interesting to consider, but they have nothing to do with what is taught in the opposed application, because it taught that mature VEGF2 was 326 amino acids. Dr. Power's experiments do not show that the invention described in the opposed application works. (HGS, for whatever reason, did not instruct Dr. Power to attempt to express mature VEGF2 with the signal peptide of the application or a heterologous signal peptide).

4.5 Dr. Mattick departed from the application even further, in declaring that he would have been motivated to express a 373 amino acid VEGF2 with a different signal peptide. (See discussion above.) Dr. Hayward's position is somewhere between Dr. Mattick and Dr. Power, because he agreed with Dr. Mattick that he could find 373 amino acids supported in the application, but discusses ways to express the 350 amino acid VEGF2. (ANH1 3.13-3.26)

4.6 One explanation given by HGS's declarants for such creative approaches was that the patent application taught that one could express VEGF2 using a heterologous leader sequence. (See ASA1 at 16; AJM1 at 4.9.) However, the ordinarily skilled scientist, wishing to use a heterologous leader sequence to

---

[7] At this point I note parenthetically that Dr. Aaronson declared Dr. Power's experiment produced "a biologically active" protein (ASA1 17). I reject this characterization. Dr. Power reported an expression study; she did not report any activity assay data.

express a secreted protein, will use that heterologous leader to *replace* the native leader sequence. (For example, in the present context one might replace amino acids 1-24 of VEGF2 with a heterologous leader sequence, attached to amino acid positions 25-350.) There is no teaching in the opposed application that one should substitute a heterologous leader to the 350 amino acid VEGF2, or to a 373 amino acid protein. Implicit in all of the experiments canvassed by the HGS declarants is that neither HGS (who designed Dr. Power's experiments) nor its declarants believe in the 326 amino acid mature VEGF2 taught by the opposed application.

D. Admissions That the VEGF2 Invention Was Incomplete

5.1 The HGS declarations plainly admitted that the declarants believe that VEGF2 as taught in the opposed application is incomplete. In a large measure, I would expect that should be the end of the Patent Office's inquiry into the issues of Lack of Fair Basis and Insufficiency, because it shows that the opposed application did not provide the public with a complete invention. As exemplified by the following excerpts several of the HGS declarants state that the beginning of the VEGF2 polynucleotide and polypeptide molecules, which notably would include the true VEGF2 signal sequence, was not present in the molecules described in the application as filed:

5.1.1 Dr. Mattick: "the fact that the signal sequence information was incomplete" AJM1 at 4.13.)[8]

5.1.2 Dr. Gamble: "I note that a portion of the full length VEGF-2 sequence, which is not disclosed in the patent specification, is part of

---

[8] Dr. Mattick also states that "An important difficulty that researchers faced in 1994 (and still face today) is the process of determining what a new gene encodes. This involves careful consideration and scientific training, and it is not a simple or straightforward process. The isolation of a DNA sequence does not establish whether the sequence encodes a protein or if it does, the nature and function of the protein it might encode. Such information had to be determined in 1994 (as it is today) by a researcher using scientific skill, their experience, their knowledge and often a wide range of different analytical and experimental tools." (AJM1 at 3.13) Dr. Mattick goes on to state that "once a DNA sequence had been cloned, further manipulations of that sequence would be relatively routine practice. Moreover once a protein sequence had been identified there were many routine methods available for analysing that protein." (AJM1 at 3.14.) At the time the opposed application was filed, however, the complete VEGF2 gene had not been cloned by HGS. Consequently, because VEGF2 as taught by the application was incomplete, if the techniques alluded to by Dr Mattick had been applied to VEGF2, I believe they would have been unproductive.

the NH2 (amino) terminal end of the full length polypeptide sequence. This equates to 69 amino acids . . . . [The VEGF-2 signal] sequence is located among the 69 amino acids that were not disclosed in the patent specification." (AJG1 at 6.4.)

5.1.3 Dr. Hayward: "The patent specification discloses 350 amino acids of the VEGF-2 sequence whereas it has subsequently been determined that VEGF-2 has 419 amino acids. The missing amino acid sequence is now known to contain the signal sequence that directs secretion of VEGF-2 from the cell." (ANH1 at 3.13.)

5.1.4 Dr. Rapoport: "[T]he 350 amino acid form of VEGF2 corresponds to amino acid residues 70 to 419 of the 419 form of VEGF2." (ATR1 at 8).

5.2 By admitting that the patent application failed to teach 69 amino acids of VEGF2, including the real signal peptide, the HGS declarants are in essence admitting that the teaching in the application that the first 24 of 350 amino acids represent a signal sequence, with mature VEGF2 being 326 amino acids, was plain wrong.

5.3 In Example 1 of the opposed application HGS purports to identify the size of the VEGF2 mRNA as 1.6kb/kd or 1.3kb. As explained in paragraph 4.13.1 of OPR1 this is just one of several errors and inconsistencies in Example 1. That is, two independent research groups (and indeed subsequent work by HGS) have demonstrated that VEGF2 mRNA is in fact 2.2-2.4kb. In paragraph 4.84-4.88 of his declaration Dr Mattick attempts to reconcile some of the inconsistencies associated with Example 1. Importantly, however, Dr Mattick does not contest the fact that the experimental results in the opposed application misinform the public about the identity and the size of VEGF2 mRNA.

5.4 As described in paragraph 4.13.2 of OPR1 the information provided in Example 2 of the opposed application is of little value to an understanding of VEGF2. I note that Dr Mattick does not contest that opinion. Paragraph 4.13.3 of OPR1 explains that Example 2 is also replete with errors and inaccuracies, and is incomplete. I find no suggestion in Dr Mattick's declaration that he disagrees with that analysis either. In fact, paragraphs 4.90-4.92 of AJM1

essentially confirm the analysis. For example, Dr Mattick admits that "there are a number of errors" in Example 2 (AJM1 4.90); that references between the description of Example 2 and the figures are "inconsistent" (AJM1 4.91); and that oligonucleotide primers are incorrectly identified and that "the patent specification fails to provide" one of the primers at all (AJM1 4.92).

5.5 Another of the HGS declarants, namely Dr. Hayward in paragraphs 4.26-4.29, also confirms that there are deficiencies in Example 2. For instance Dr Hayward admits that it would not be possible to use the F4 primer (part of primer pair 2) to make the polypeptide that was allegedly made. Furthermore, apparently in order to comment on Example 2, Dr Hayward departs from the teaching in the opposed application and interprets that F4 as taught in Example 2 is really F5, and that F4 is missing. Whilst Dr. Hayward states that he would have been able to carry out experiments similar to those shown in Example 2, that does not alter the fact that the description of Example 2 is inadequate, necessitating the reader to experiment even if all that the reader desired was to repeat the "Examples".

E. The Opposed Application Is an Invitation to Experiment, Not a Complete Invention.

6.1 Even though the HGS declarants admit that the opposed application describes VEGF2 incorrectly, they still try to rehabilitate the application as a starting point for research. As I explained above, many of the HGS declarants try to explain how they would have eventually experimented to make alternate molecules (e.g., foreign signal sequences attached to either a 350 amino acid VEGF2 or a 373 amino acid VEGF2) that the opposed application simply fails to teach. Such experimentation is beyond the teachings of the application, and involves an amount of work that is orders of magnitude greater in time and complexity than the relatively straight-forward partial cloning and sequencing work of the application.

6.2 In this regard, the repeated attempts by the HGS declarants to rehabilitate the opposed application constitute a considerable proportion of the evidence-in-

answer. Appendix I to this declaration (which reproduces Exhibit PAWR-9 of OPR-2) lists some of the many references in the evidence in answer to experiments that the HGS declarants might have thought to perform in 1994, had they been provided with the teachings of the opposed application. My understanding is that the HGS declarants believe such extensive experimentation would have been necessary in order to try to make or use the VEGF2 invention.

6.3 Such an admission by the HGS declarants validates my opinion that the disclosure in the patent application is inadequate to give to the public what is claimed as the invention. Put simply, the experimentation recommended by the HGS declarants would not be necessary if the invention worked in the manner described in the opposed application. A considerable amount of the experimentation suggested by the HGS declarants is devoted to firstly determining that the application was wrong, and then to how it might be corrected. I also find it notable that the HGS declarants for the most part have not actually performed the experimentation to see if it would work. In any case if all of the experimentation would have eventually resulted in a working invention, it would no longer be the invention of the opposed application.

6.4 Dr. Mattick states that the VEGF2 sequence information in the patent application "would have allowed me and I believe any person of ordinary skill in the field of molecular biology in 1994 to design specific strategies to obtain any polynucleotide sequence (ie gDNA, mRNA or cDNA) encoding VEGF-2." (AJM1 at 3.34) Dr. Hayward makes a similar declaration. (ANH1 at 3.26 and 4.18.) In relation to those statements I have two comments. First, Dr Mattick's opinion that the skilled person could "design strategies" carries with it no guarantee of a successful result, the skilled person is merely designing experiments for further research. Second, the necessity for the skilled person to introduce "strategies" beyond those described in the patent application only arises because the invention does not work the way that HGS taught.

6.5 In the context of this discussion of the inadequacy of the opposed application I find it interesting that HGS filed a new series of patent applications when they

eventually isolated a full-length VEGF2 sequence of 419 amino acids. [*See* Documents D44-46 and discussion at OPR1 paragraphs 1.5.1.1-1.5.3.] As Dr. Mattick and Dr. Hayward appear to believe that "any" VEGF2 polynucleotide sequence might be obtained on the basis of the disclosure in the opposed application by a person of ordinary skill using routine methods, it follows that they would believe that HGS's second series of VEGF2 patent applications must lack inventiveness.

6.6 According to Dr. Mattick and Dr. Hayward the disclosure regarding VEGF2 in the opposed patent application was sufficient to identify and isolate VEGF2 from other species. (*See* AJM1 4.93-4.94; ANH1 at 4.19.) I cannot agree with Dr. Mattick and Dr. Hayward's evaluation. On the contrary, in my opinion, the disclosure regarding VEGF2 fails even to provide the public with complete human VEGF2 (see OPR1 at, e.g., 1.5.1.1 and 4.11-4.11.1.3.) and so, clearly, cannot be said to provide the public with VEGF2 from other species. It would have been a much greater leap from incomplete human VEGF2 to complete VEGF2 from other animals. In fact, when HGS eventually discovered full length human VEGF2, they believed that the discovery was of sufficient magnitude to warrant another series of patent applications (as set out in paragraph 6.5 above) thus, appearing to bear out my opinion of the inadequacy of the opposed application.

F. Experimentation Regarding VEGF2 Biological Activity

7.1 Many of the preceding sections of my declaration address the substantial experimentation that HGS admits in its evidence in answer would be required simply to express VEGF2 polypeptides (which, as I have explained, are not the polypeptide taught in the opposed application). However polypeptides *per se* are not necessarily useful for anything more than questions for further research, so expression of a VEGF2 polypeptide represents only part of the experimentation necessary to practice the VEGF2 invention. The evidence in answer clearly envisages that extensive further experimentation was needed to determine exactly what VEGF2 biological activity is.

7.2 Neither the opposed application nor the HGS declarations present any actual scientific evidence that VEGF2 as taught in the opposed application has any biological activity.

7.3 Dr. Mattick alleges that VEGF2 activity for promoting growth of endothelial cell cultures has been validated for VEGF2:

> "I note that such an activity has subsequently been shown to be something possessed by VEGF-2. I refer to HGS Patent Application 60467/96 (714,484), which shows that VEGF-2 exhibits proliferative effects on vascular endothelial cells (see page 42, line 32 to page 43 line 25 and Figures 8 and 9)." (AJM1 4.15)

7.4 In terms of the opposed application, however, it must be noted that the VEGF2 purportedly tested in Patent Application 714484 is not the same VEGF2 that HGS taught in the opposed application. I do not know whether Dr. Mattick simply overlooked this fact or whether he considers it an insignificant difference. In any case the fact that HGS filed the second VEGF2 patent application suggests to me that they felt that it was significant. On the basis of my understanding of their declarations, I believe that any conclusions regarding the biological activity of 326 amino acid mature VEGF2 of the opposed application which are based on data derived from what was allegedly an approximately 374 amino acid VEGF2 would be rebuked by HGS's declarants (e.g., Dr. Gamble) as highly speculative. It is simply not sound scientific reasoning to rely on the excerpts cited by Dr. Mattick to conclude that VEGF2 taught in the opposed application is useful for endothelial cell culture.

7.5 Dr. Mattick, Dr. Gamble, and Dr. Hayward all cite Example 1 of the opposed application as allegedly providing evidence for VEGF2 biological activity:

7.5.1 Dr. Mattick: "Further the patent specification provides in Example 1 Northern Blot data (see figure 4) showing that VEGF-2 is over-expressed in breast cancer cell lines. This result indicates to me that VEGF-2 is biologically active in tumours." (AJM1 at 4.18.)

7.5.2 Dr. Gamble: ". . . confirmation that the VEGF-2 sequence described in the specification is expressed in vivo, and therefore likely to indicate a biological activity, is provided in the Examples of the specification where it is shown by Northern blotting that a number of malignant breast tumour cell lines over express VEGF-2. The over expression of VEGF-2 in breast cancer cell lines while absent in a normal breast sample suggests a role of VEGF-2 in tumour development perhaps by promoting the growth of new blood vessels, as was observed for VEGF. (AJG1 7.17. See also AJG1 7.28 - 7.29)

7.5.3 Dr. Hayward: "In Example 1 in the patent specification the inventors demonstrate that VEGF-2 is over expressed in vivo in a number of malignant breast tumour cell lines. This result is, I believe, indicative of VEGF-2 biological activity. It suggests to me that VEGF-2 plays a role in tumour development possibly by promoting new blood vessel growth similar to VEGF. Additionally, it is apparent to me from reading the patent specification as I believe it would be to others in my field that VEGF-2 is a growth factor that is related to VEGF and is likely to play a role in the regulation of endothelial cell mitogenesis." (ANH1 at 4.6)

7.6 However, numerous problems are associated with the conclusions advanced by Dr. Mattick, Dr. Gamble, and Dr. Hayward.

7.7 Assuming that VEGF2 is active in tumours, Example 1 provides no indication of which form of VEGF2 molecule might be involved. A Northern hybridization study of the type described in Example 1, even if performed correctly, would not indicate to a scientist what protein forms are present. To elaborate, it is now well established and admitted by HGS that the VEGF2 taught in the opposed application is incomplete, yet HGS has produced no evidence that the incomplete VEGF2 is expressed and/or secreted in any human cells. In contrast, Dr. Alitalo's publications relating to VEGF-C indicate that the polypeptides which are expressed *in vivo* are very different to that taught in the opposed application. (See, e.g., Documents D71-D74 and discussion above.) Significantly, the two declarations by Dr Alitalo demonstrate that the VEGF2 of the opposed application is not expressed and

secreted by cells. (See OKA1 and OKA2.) It is scientifically unsound to assume, as Dr Mattick, Dr Gamble and Dr Hayward have done, that the incomplete VEGF2 of the opposed application must be involved in the tumour cells assayed in Example 1 of the patent application.

7.8 Northern hybridization, when performed correctly, can show whether a specific RNA is present in a sample, and may provide an indication how much of that RNA is present in the sample. Northern hybridization, however, is not a sound basis for any scientist to speculate as to what the activity of the polypeptide encoded by an RNA actually is. Thus even if Dr. Mattick, Dr. Gamble, and Dr. Hayward are correct in concluding from Example 1 that VEGF2 is biologically active in tumours, it is not possible for them or anybody else to say what that activity actually is. There are a myriad of possibilities that may be speculated to explain why (if indeed they are) the tumours are secreting VEGF2, including the following: as an autocrine growth factor, to inhibit further growth of tumour cells, to stimulate or inhibit growth of some other tissue type, to kill healthy cells to make room for tumour growth, to recruit a different cell type(s) to the tumour, to inhibit immune cells such as tumour infiltrating lymphocytes from attacking the tumour, or any of many other possible activities. Without a considerable amount of additional experimentation it is not possible to determine which of these possible activities, if any, the VEGF2 may be having. A Northern blot study provides no more than indirect evidence that a cell might be making a particular protein. To use Dr. Gamble's words, any conclusion about VEGF2 activity based on a Northern hybridization study, "cannot reasonably be drawn" and is "pure speculation".

7.9 The OPR1 declaration discussed published evidence (largely from Dr. Alitalo's research group) indicating that a principle activity of the real-life protein product of the VEGF2 gene (i.e., VEGF-C) in healthy mammals appears to be a growth factor for the lymphatic vessels.[9] This fact appears uncontested in HGS's evidence-in-answer. Notwithstanding the numerous

activities prophesied for VEGF2 in the opposed application, the inventors failed to teach that VEGF2 was a lymphatic growth factor. The HGS declarants do not assert that they learned from the application to use VEGF2 as a lymphatic growth factor.

7.10 In summary, the evidence-in-answer is replete with explanations of how the declarants believe that they could have performed experiments to determine that the opposed application incorrectly characterised VEGF2. Many of the experiments proposed by the HGS declarants would have required ingenuity to contravene the plain teachings in the application, after experimentally determining that the invention does not work as taught. The HGS declarants go on to state that they believe that they could, after departing from the wrong teachings of the application, have performed additional experimentation to correctly characterise VEGF2 and then use it for whatever purposes their experimentation revealed VEGF2 could be used for. The position that the evidence-in-answer appears to support is that HGS should be granted a patent because the application would have aroused curiosity which, when combined with a scientist's enthusiasm to experiment, might have stimulated substantial further experimentation which might have uncovered the inaccuracies in the application and revealed that the invention does not work as described, and which might have led to alternatives or improvements not taught in the application that might have worked. In my opinion it would not be fair to grant a patent on the basis of an application that teaches an incomplete and incorrect invention that others might eventually be able to rectify, complete and use. The patent application should be judged on what it teaches, rather than on how other scientists feel they could apply further experimentation to overcome its substantial shortcomings and errors. The fact that such experimentation might have revealed the inaccuracies in the opposed application or revealed alternative inventions to the invention described therein does not rectify the errors and inadequacies of the application. In this context, it bears repeating that HGS filed a second set of VEGF2 patent applications after identifying inadequacies in the opposed application, and that Dr. Alitalo's group, which

---

[9] As indicated in OPR1 at 4.7, the opposed application fails to teach the actual protein product

did much of the actual science, has been awarded their own patents for their ingenuity relating to VEGF-C.

7.11 Substantial parts of the evidence-in-answer are spent discussing general molecular biological techniques said to be taught in the opposed application (e.g., AJM1 at 3.12-3.19; 3.29, 3.31, 4.71; and 4.83; AJG 6.8-6.8.11; ANH1 at 3.6, 3.11, 3.21). The many deficiencies of the opposed application are not overcome by merely referring to standard molecular biological techniques needed to conduct further experimentation. Regardless of the emphasis HGS places in the evidence in answer on stock teachings in the application, they remain nothing more than an invitation to experiment rather than teaching of a complete VEGF2 invention. The amount of experimentation that HGS conducted and included in the application is insignificant compared to the experimentation required of the Australian public to determine the true structure of the VEGF2 gene and protein, a workable method of expressing and secreting the protein, and a proper identification of its biological activities. That remaining experimentation to make the invention work in the manner taught by the application is not merely routine in nature. Rather, it is experimentation to discover features not described in the application, and then experimentation to make it work.

7.12 Much of the evidence-in-answer is devoted to repeating various unsupported predictions in the patent application. A selection of these is listed in Appendix II of this declaration (which reproduces Exhibit PAWR-10 of OPR2). The OPR1 declaration acknowledged that the patent application contains such predictions. (OPR1 at 2.3.3 and 4.6.5.) It also explained that these were predictions lacking any apparent basis in scientific experiments (OPR1 at 4.6.3.1 and 4.6.5.) or other accepted scientific basis. (OPR1 at 4.6.3.1 and 4.6.5.) The evidence-in-support also included scientific evidence that many of the predictions were incorrect. (OPR1 at 4.6.4 and 4.6.5.) The many specific deficiencies of the patent application are not overcome by having experts repeat the inventors' predictions in the evidence-in-answer,

---

of the VEGF2 gene.

without critical evaluation of whether the predictions are soundly based in fact.

G. Inappropriate Use of Hindsight in the Evidence-in-Answer

8.1 I cannot agree with substantial parts of the evidence-in-answer because the conclusions made by the HGS declarants are based on what is now known about VEGF2 and VEGF-C. That current knowledge arises from scientific literature and patents published after the filing date of the opposed application. This hindsight interpretation by the HGS declarants is entirely inappropriate. Herein I explain the hindsight and consider an analysis which only involves the common general knowledge as it existed in 1994, combined with what is disclosed in the opposed application. Again, I have focused my remarks principally on issues relating to protein structure and protein expression.

8.2 In paragraphs 3.22 and 4.7 Dr. Mattick concludes that "the nucleotide sequence disclosed in Figure 1 may also be read to encode an additional 23 amino acids" despite the fact that the opposed application teaches that VEGF2 contains only about 350 amino acids. Dr. Hayward drew a similar conclusion. (ANH1 at 3.14 and 4.18.) As I explained above, such conclusions are contrary to the plain teachings of the opposed application. Dr Mattick's and Dr Hayward's conclusions can only be made if they introduce the teachings of documents published after the opposed application, namely, those that show that VEGF2 includes additional amino acids. As a consequence, their analysis is based on hindsight.

8.2.1 Dr. Mattick and Dr. Hayward refer to Figure 1 of the opposed application. Figure 1 depicts a DNA sequence and a deduced VEGF2 protein sequence. The opposed application states: "Fig. 1 depicts the polynucleotide sequence which encodes for VEGF2, and the corresponding deduced amino acid sequence of the full length VEGF2 polypeptide comprising 350 amino acid residues of which approximately the first 24 amino acids represent the leader." (p. 4, lines 28-32.) I find no ambiguity in the opposed application with

respect to the length of full length VEGF2. In addition, there is no ambiguity in the opposed application regarding the location of the methionine codon (ATG) at the beginning of the VEGF2 protein-encoding sequence: it is at approximately positions 71-73 of the DNA sequence in Figure 1. The opposed application thus explicitly teaches the location at which full length VEGF2 begins. There is also a clear statement identifying the division between the 24 amino acid signal peptide and the "mature" VEGF2 of 326 amino acids.

8.2.2 Subsequent work by multiple groups, including the inventors of the patent application, contradicted the position that the protein encoded by the VEGF2 gene is only about 350 amino acids. As subsequently shown, the protein is about 419 amino acids. The opposed application failed to teach about 69 amino acids at the beginning of the protein [see OPR1 at 4.11.1-4.11.3 (citing Documents D43, D44-46, D84-86 of HGS; D75 and D84 of Genentech; and D71-D74 of University of Helsinki.)][10] Thus, whilst I can explain how Dr. Mattick and Dr. Hayward were able to conclude that the Figure 1 sequence might actually encode more than 350 amino acids, such a conclusion is clearly biased by what is now known, and is contrary to what the patent application actually teaches.

8.3 Dr. Mattick's reliance on hindsight is also clear in the following passage:

> "Taking into account the existence of the additional 23 amino acids at the N-terminal end of the VEGF-2 sequence disclosed in the patent specification, I would also have stitched a signal secretion sequence to the beginning of the cDNA disclosed in the patent specification, as is taught in the patent specification. I note that such an experiment was done and is described in

[10] In addition, the 373 residue VEGF2, which has no basis in the application, also has no apparent significance in human biology. The evidence-in-answer acknowledges that full length

Australian Patent Application 60467/96 (714,484) (HGS' second VEGF-2 patent application) and the resultant product from those experiments is reported to be biologically active (see page 42, line 32 to page 43 line 25 and Figures 8 and 9 -- HGS' second VEGF-2 patent application)". (AJM1 4.8).

8.4 Dr Mattick's hindsight approach with respect to the "additional 23 amino acids" not taught in the application is further imported from reading HGS's second VEGF2 application, attaching a signal peptide to the beginning of the additional 23 amino acids. In so far as the opposed application suggests that a foreign signal peptide might be attached to a VEGF2 sequence, it is clear to me that the suggestion would have been to attach it to "mature VEGF2", which the application teaches is only about 326 amino acids in length (see opposed application at pp. 4-7). I repeat that the additional 23 amino acids are not taught in the opposed application. On the contrary, the application teaches that the relevant polynucleotide sequence contained 69 nucleotides of noncoding sequence preceding the position 1 methionine. The patent application taught that a true signal sequence immediately followed the 69 nucleotides of noncoding sequence. As polypeptides do not need two signal peptides for expression and secretion it would have been highly irregular for any scientist in 1994 (or even now) to attempt to attach a signal peptide-encoding sequence to 69 nucleotides of noncoding sequence, because it would be highly unusual to drive expression of noncoding sequences using signal sequences.

8.5 Three pages of Dr. Mattick's declaration are directed to explaining how to express VEGF2 using "routine trial and experimentation." However, Dr. Mattick's explanation begins with the following assumption which indicates clearly his further reliance on hindsight:

VEGF2 (with signal sequence) is 419 residues. Professor Alitalo's research group has demonstrated that the 373 residue molecule is substantially different to the forms secreted by human cells.

> "Had I attempted to express the VEGF-2 protein using the putative secretion signal sequence identified in the patent specification and had that not worked . . . ." (AJM1 4.5.)

8.5.1 The beginning of Dr. Hayward's analysis indicates a similar vantage point. (See ANH1 at 3.17.)

8.5.2 Such a starting point is adopted by the HGS declarants because, with the benefit of hindsight knowledge, they are aware that the signal sequence taught in the opposed application is ineffectual and that the scientific literature of the last four years has essentially ignored the 350/326 teachings of the opposed application. At the time of filing the opposed application, however, I can see no reason why a scientist with ordinary knowledge would have known that the signal sequence it taught would not work. Such a scientist attempting to work the invention would have read the description in the application relating to the sequence listing, attempted to express the polypeptide following the description, and failed. The person might have repeated the experiment and might have modified any of a number of parameters (such as promoter, cell type, expression vector, growth conditions, to name a few) in an attempt to discover why things did not work as taught. Extensive experimentation might have been required in order to arrive at the true source of the problem and its solution.

8.6 A similar reliance on hindsight is apparent in the statements by Drs. Gamble, Hayward, and Rapoport that, regardless that the VEGF2 taught in the opposed application is incomplete and that portion of the sequence described as the signal is incorrect, they would have apparently expected to be able to express and secrete VEGF2 successfully. In order to do so each suggests attaching a heterologous (foreign) signal sequence to the 350 amino acids of VEGF2 that were taught in the patent application. (See AJG1 at 6.5; ANH1 at 3.20-3.22; ATR1 at 13.) Dr. Power reports performing such an experiment under instructions from HGS (ASP1), and Dr. Aaronson approves of her experiment. (See, e.g., ASA1 at 15-22).

8.7 The idea of expressing the 350 amino acid VEGF2 taught in the patent application with a foreign signal peptide has nothing to do with the teachings in the opposed patent application. The patent application teaches that the VEGF2 consists of about 350 amino acids of which the first approximately 24 amino acids is a leader (signal) sequence, and the mature protein is 326 amino acids. (See, e.g., page 5 of the opposed application.) There would be no reason, either in 1994 or today, to attach a heterologous (foreign) signal sequence (e.g., Dr. Power's Ig Kappa signal sequence) to the beginning of a natural signal sequence in order to express the protein. Neither Dr Power's experiment nor the hypothetical experiments suggested by other HGS declarants replicate any of the examples in the opposed application, nor do I consider them a reasonable extension of any of the application's teachings. In fact, the instructions given to Dr Power amount to a direction not to replicate the patent teachings. (ASP1 at 2.) The instructions given to Dr. Power to my mind represent an admission by HGS that the alleged invention taught in the opposed application does not work the way that the application taught it would.

8.8 In terms of suggestions to perform the experiment in which a foreign signal sequence is attached to the 350 amino acid VEGF2, the only ones which come to mind are from scientific papers and patent literature regarding VEGF-C or VEGF2 published after the filing date of the opposed application. It is that literature which teaches that the gene actually has 419 codons, and that the 350 codon sequence taught in the opposed application was incomplete and lacked a signal peptide. (*See* OPR1 at, e.g., 1.5.1.1 and 4.11-4.11.1.3; ATR1 at 8.)

8.9 Hindsight also clouds Dr. Rapoport's analysis of the signal peptide issue. For instance, Dr. Rapoport is of the opinion that it was known that signal sequences located at the N-terminus of proteins "were required to direct secreted proteins outside of the cell." (ATR1 at 4). In his opinion, researchers were able to characterise such sequences by inspection or using software. (ATR1 at 5-6). Dr. Rapoport states that he does not observe a typical conserved motif of a signal sequence in the 350 amino acid VEGF2 taught in

the opposed application. (ATR1 at 10.) Given Dr Rapoport's comments in paragraphs 4-6 relating to signal sequences, a reasonable expectation is that Dr. Rapoport would therefore conclude that VEGF2 was not secreted at all.

8.10 On the contrary, Dr. Rapoport goes on to state that there was "strong evidence" that the 350 amino acid VEGF2 was a secreted protein "based on the teaching and recognition of the HGS specification that it is a member of a family of secreted growth factors." (ATR1 at 10 and 7.) I cannot, and I believe most scientists experienced in molecular biology in 1994 would not, agree that the opposed application provides the "strong evidence" upon which Dr Rapoport bases his further statements. The only "evidence" offered by the opposed application is the recognition that VEGF2 exhibited 22-30% identity with VEGF and the PDGF proteins. (ATR1 at 7, 9.) As explained in detail in the OPR1 declaration and not contested by any of the HGS declarants, such a low level of sequence identity is not conducive to reliable prediction of structure or function. (See OPR1 at 4.63-4.65.) There are many examples in the literature of proteins with significantly greater structural similarity, but divergent function. Rather, the examples in OPR1 demonstrate that 22-30% sequence similarity is insufficient to allow one confidently to conclude that two proteins are both growth factors, or are both secreted from cells.

8.11 In my opinion, the motivation for the hypothetical experiments described by Dr. Rapoport arises from a knowledge of the 419 amino acid VEGF2 (ATR1 at 8) and published information about VEGF-C (ATR1 at 13-17), coupled with the partial description in the opposed application, in a desire to make something work. Dr Rapoport's statements as to what he would have predicted and/or expected and/or recognised based solely on the patent application do not withstand scrutiny.

H. Reply to AJM1 4.96-4.102 and AJG1 6.8.1-6.8.2.

9.1 The opposed application gives no indication that HGS intended to claim the particular sequences of claims 11-12, 32-35, and 40-41. The description simply provided observations that these portions of VEGF2 represented

portions sharing conserved motifs with the prior art, but they were not described as discrete peptides. (See OPR1 at 5.8.1 - 5.8.6) Dr. Mattick infers this intention from identification of conserved motifs at page 5 and Figure 2, which he combines with the teaching at page 9 about "fragments of VEGF-2." I do not consider Dr Mattick's analysis persuasive.

9.2 According to my reading of page 9 of the opposed application, there is no mention of conserved motifs or of the alleged "signature" sequence. According to my reading of page 5 and Figure 2, there is a discussion of the signature motifs but no mention of VEGF2 fragments of the invention. I note an observation that VEGF2 shares two characteristics with VEGF and PDGF, but neither of those characteristics is a VEGF2 "fragment." To explain further, the first characteristic – eight conserved cysteines – are scattered throughout the VEGF2 sequence, but are not a fragment of it. The second characteristic is a generic chemical formula PXCVXXXRCXGCCN, again not a VEGF2 fragment. Thus, nowhere in the application is the "signature for the PDGF/VEGF family" stated to represent a "VEGF2 fragment" of the invention.

9.3 In paragraph 6.8.1 - 6.8.2 Dr. Gamble summarily states that she believes that the patent specification provides "a range of different length VEGF-2 polypeptides," as well as the DNAs encoding them. For reasons explained in OPR1 and in the preceding paragraphs, I disagree.

I. Additional Observations

10.1 The evidence in answer includes a brief explanation by Dr. Aaronson that if, in March 1994, he had a novel 350 amino acid VEGF2 sequence, he would have predicted (a) that it was proteolytically processed; and (b) that it was biologically active. (See ASA1 at 5 - 6.) Dr. Gamble declares that she would make similar predictions. (See AJG1 at 6.5.) In my opinion, the relevant issue is what the patent application says and whether or not it is correct, rather than whether Dr. Aaronson or anyone else would have made favourable or unfavourable "predictions."

10.2 As I have discussed above, the HGS scientists also predicted proteolytic processing in a way comparable to what was known for VEGF. They were wrong. As a result, what they taught the public through the patent application was also wrong. First, the VEGF2 sequence as taught was incomplete, and is not processed in the way that the HGS inventors or Dr. Aaronson predicted. Second, the HGS scientists still predicted wrongly when they later became aware of the full 419 amino acid VEGF2. Dr. Alitalo's publications demonstrate that proteolytic processing of VEGF-C is considerably more complicated than the proteolytic processing that occurs with VEGF. (See **Document D71** and Figure 1 which is **Exhibit FJB-1** hereto.)

10.3 Despite the declarations by HGS's experts that the requisite testing for activity would have been "routine" (see, e.g., ANH1 at 4.7) there is absolutely no evidence in the patent application or the ensuing literature that has been made of record in this proceeding that the VEGF2 taught in the opposed application is "biologically active." HGS has apparently reported activity data only for molecules that were taught in its subsequent application and for molecules taught by other research groups (e.g., Alitalo *et al.* for VEGF-C).

10.4 In paragraph 3.29 Dr. Hayward declares that VEGF-2 "of course" functions as a growth factor. This, too, has never been established. Certain growth factor activities have been reported for the VEGF-C forms described by Professor Alitalo and his colleagues. The later HGS application alleges that a form of VEGF2 (which is not identified in that application) may have exhibited some growth factor activity in some experiments. However, neither the VEGF-C polypeptides of Alitalo nor the 419 amino acid VEGF2 from that later HGS application are taught in the opposed application.

LACK OF NOVELTY AND INVENTIVE STEP OF CLAIMS OF THE OPPOSED APPLICATION

11.1 When addressing novelty and inventiveness, the HGS declarants consistently failed to identify any explicit claim language that excludes the prior art from the claims. I maintain my original opinion, an opinion shared by Dr. Rogers

and set out in OPR1, that most or all of the claims encompass the prior works of others. Below, I explain in detail one example of why the claims read on the prior art, and why the HGS declarants have failed to effectively rebut this fact. The example on which I focus relates to the claims that appear intended to encompass VEGF2 "fragments, analogs, and derivatives."

A. Review of the Grounds of Opposition

11.2 The OPR1 declaration, in particular section 2, indicated that at least claims 1-4, 13-28, and 34-61 of the patent application encompassed materials and methods that had been disclosed by others in literature published before HGS's earliest alleged priority date of 8 March 1994. Whilst that earlier literature may not have described the exact VEGF2 DNA or deduced amino acid sequences as per the figures or sequence listing of the opposed application, the relevant claims are not so limited. In my opinion, the claims as they presently stand embrace these other sequences.

11.3 For example, several claims in the opposed application are directed to a "fragment, analog or derivative" of a VEGF2 polypeptide (*e.g.*, claim 28) or to a polynucleotide encoding a "fragment, analog or derivative" of a VEGF2 polypeptide (*e.g.*, claims 1-4, 21). The opposed application says that fragments, derivatives, or analogues may be VEGF2 polypeptides modified such that one or more of the amino acid residues of VEGF2 are substituted with conserved or non-conserved amino acid residues, and/or ones in which additional amino acids are fused to the mature polypeptide. (See, *e.g.*, pp. 9-10.) Also, polypeptides resulting from deletion of amino acids would also seem to be within the commonly accepted definition of "fragment, analog, or derivative." (See page 7 of the opposed application discussing "deletion variants, substitution variants, and addition or insertion variants.") Because the claims embrace molecules with changes, additions, or deletions to the VEGF2 sequence, it is clear that they are intended to cover more than simply the exact sequences taught in the application.

11.4 The prior art literature identified in OPR1 describes DNAs and polypeptides, such as VEGF, PlGF, PDGF-a, and PDGF-b, that differ from the exact VEGF2 DNA and amino acid sequences of the opposed application, but only in ways that are embraced by the application's definition of "fragment, analog, or derivative." (See OPR1 at 2.2-2.2.2, 2.3, 2.7.1, 2.7.9, and 2.7.20.) In other words all of the structural differences between a VEGF sequence and a VEGF2 sequence can be classified as either additions, deletions, or conservative or non-conservative substitutions.

11.5 The patent application states that "It is particularly important that all eight cysteines are conserved within all four members of the family" (PDGFa, PDGFb, VEGF, and VEGF2). (See page 5.) Importantly, it is these eight cysteines that are the only amino acids that the application seems to say should not be changed when designing VEGF2 fragments, analogues, or derivatives. However, this comment in the application would not serve to exclude the prior art members of the family from the claims, because the eight cysteines are a common feature between VEGF2 and the prior art PDGF and VEGF polypeptides.

11.6 Because the list of modifications and alterations to VEGF2 embraced by fragments, analogues, or derivatives would embrace the differences between VEGF2 and the prior art VEGF, PlGF, and PDGF polynucleotides and polypeptides, and there are no apparent restrictions in the specification or claims about the number of changes that can be made, except perhaps the eight conserved cysteines, all of these prior art molecules could fairly be classified as VEGF2 fragments, analogues, or derivatives. (See, e.g., OPR1 at 2.2 - 2.2.2.) The claims are unrestricted in terms of the number of modifications to the VEGF2 sequence that a fragment, analogue, or derivative can contain, with the result that, VEGF2 could theoretically be modified until it matched VEGF, PlGF, or PDGF.

B. Review and Reply to HGS Evidence-in-Answer

11.7 The HGS Evidence-in-Answer contains no considered rebuttal of the analysis in OPR1 that the claims are not explicitly restricted in such a way that the meaning of "fragment, analog, or derivative" excludes prior art polynucleotides and polypeptides such as VEGF, PDGFa, PDGFb, and PlGF (as described in the literature cited in OPR1). On the contrary, in paragraph 4.37, Dr. Mattick essentially admits that *the claims* do not set a maximum number of modifications that can be made to a protein that is to be classified as a VEGF2 fragment, analogue, or derivative; it appears that Dr. Mattick simply would not require such a clear definition.

11.8 The HGS declarants instead propose a subjective "looks more like" approach for interpreting the claims in a manner which allows them to exclude VEGF, PDGFa, and PDGFb from the claims.

11.8.1 For instance, Dr. Mattick states: "I would not require the patent specification to set a maximum limit of modifications that can be made to a protein before I could reasonably ascertain whether a protein was a fragment, analogue, and/or derivative of VEGF-2. . . . As soon as a protein starts to look more like VEGF, PDGFa, PDGFb, or PlGF, it would not, in my opinion, be a fragment, analogue and/or derivative of VEGF-2. Thus, I would not regard any of VEGF, PlGF, PDGFa or PDGFb to be VEGF-2 fragments, analogues and/or derivatives." (AJM1 4.37; see also AJM1 4.26.)

11.8.2 Similarly, Dr. Gamble states: "For something to be a fragment, derivative or analogue of a molecule it must not only share a biological function or activity with VEGF-2 but it must also have homology at the primary amino acid level. Thus, a peptide or polypeptide that more closely resembles VEGF, PDGFa, PDGFb or PlGF, than VEGF-2 at the primary amino acid level would not be a VEGF-2 fragment, derivative or analogue. Such an interpretation is inherent in the meaning of these terms and is consistent with the general manner in which others and I use these terms in everyday scientific language." (AJG1 at 7.12. See also AJG1 7.25 - 7.27)

11.8.3 Dr. Hayward says that "there is not sufficient sequence identity between VEGF2 and PDGF, VEGF, and PlGF for these molecules to be considered derivatives of VEGF2". (See, e.g., ANH1 at 3.8, 4.2.) Dr. Hayward does not explain what minimum sequence identity would be required for him to consider them to be derivatives and, in any case, the claims do not include a minimum sequence identity.

11.9 The "looks more like" approach adopted by the HGS declarants is completely subjective, and is vague as a consequence. This "looks more like" standard is not described in the opposed application, and implementing it would result in the scope of the claims changing over time. Put simply, such an approach is unworkable.

11.10 Such a vague and subjective approach is contrary to my understanding of patent law as explained to me by Ludwig Institute's attorneys. It is my understanding that the scope of each claim is required to be clearly defined so that the reader can determine whether or not something falls within a claim.

11.11 To elaborate further, there are no clear reference standards in the opposed application or the field of the invention which would allow a reader to determine whether a theoretical analogue "looks more like" VEGF or VEGF2. When working with proteins, such a "looks like" criteria might be based on any one (or any combination) of a number of criteria, such as percent amino acid similarity, three-dimensional shape, size, or potentially on more subtle criteria, such as whether amino acids predicted to be essential for activity of the polypeptide are more like those found in VEGF or VEGF2.

11.11.1 To illustrate the unworkability of the "looks more like" approach, an approximately 190 amino acid stretch of VEGF2 shares homology with a silk protein. (See OPR1 at 4.11.1.3 and **Document D71**, Joukov *et al.*, EMBO J 16:3898-3911(1997)) If most or all of this portion of VEGF2 were removed the result would be a VEGF2 much more similar in size to that of VEGF. The folded shape of the truncated VEGF2 may look more like the three-dimensional shape of VEGF polypeptides having a similar size. However, such a fragment would still have 100% amino acid identity with a portion of VEGF2 and much lower amino acid identity with VEGF. Given such a scenario, it is impossible to determine with any confidence, using the "looks like" criteria, whether or

not the molecule falls within the claims of the opposed application.

11.11.2 To further illustrate the inexactitude of the HGS "looks like" approach, I note that mature VEGF-C has an amino acid sequence which is nearly identical to a portion of VEGF2, if the approximately 190 BR3P-like amino acids are removed from the C-terminus, and still more amino acids are removed from the N-terminus of VEGF2. Whilst this molecule will bind VEGFR-2 (one of the two VEGF receptors) VEGF2 will not. (See OPR1 at 4.11.1.3 and Joukov *et al.*, EMBO J 16:3898-3911(1997).) Thus, if the "looks like" approach is adopted there are at least two competing criteria by which VEGF-C might be classified: due to the amino acid sequence identity it might be classified as a VEGF2 analogue; alternatively because of receptor binding properties it might be classified as a VEGF analogue.

11.12 It bears repeating that the "looks more like" standard for defining the term "fragment, analog, or derivative" is not apparent on any fair reading of the opposed application. In fact, the opposed application doesn't provide any standard, nor does it limit the number of sequence changes that are encompassed within the term.

11.13 Further compounding the unworkability of HGS's "looks more like" approach is that the discovery of new genes would lead to changes in the meaning of the term "fragment, analog, or derivative" which in turn would lead to changes to the scope of the claims. I can illustrate this problem with the following two examples.

11.13.1 Figure 3 of the opposed application shows that the VEGF2 sequence more closely resembled VEGF (30% amino acid identity) than any other protein known at March 1994 at the primary amino acid level. VEGF2 thus looked more like VEGF

than other known molecules and so, using the HGS "looks more like" standard would, in March 1994, have been characterised as a "VEGF fragment, analog, or derivative".

11.13.2 The second example is that of the VEGF-D gene and protein first described by Achen *et al.* (See OPR1 at 4.12.1; and Document D67.) VEGF-D has a higher per cent amino acid identity to VEGF2 than it has to VEGF and so, using the HGS "looks more like" standard, might be considered to fall within the HGS claims. However, VEGF-D is a distinct human protein in its own right, encoded by its own gene, and its discovery owes nothing to the discovery of VEGF2. (See OPR1 at 4.12.1.) Thus, it would be just as illogical to call VEGF-D an analogue or derivative of VEGF2 as it would have been to call VEGF2 a mere analogue or derivative of VEGF, when VEGF2 was discovered (due to shared amino acid motifs and allegedly shared biological activities).

11.13.3 Therefore, analysis of what might occur under HGS's "looks more like" approach indicates that the scope of HGS's patent claims narrows with the discovery of each new gene family member (such as VEGF-D). Before VEGF2 was discovered, all of the analogues that looked more like VEGF than PDGF would have been called VEGF analogues. When VEGF2 was subsequently discovered, all of the VEGF analogues that looked more like VEGF2 than VEGF (or the PDGFs) would have been reclassified as "VEGF2 analogues". That classification, however, would also have been temporary since, when VEGF-D was discovered, some of those analogues would be more similar to VEGF-D than VEGF, VEGF2, or the PDGFs and so would be re-classified as VEGF-D analogues. As is apparent in this example the breadth of the claim is narrowed every time a new member of the VEGF family is discovered. The idea that the scope of patent claims changes

with each new VEGF family member is contrary to my understanding of the requirement that the claims clearly define the scope of the patentee's monopoly.

11.14 Thus, in summary, the literal scope of "fragment, analog, or derivative" claims embraces VEGF, PDGFa, PDGFb, and other subject matter identified in OPR1 that was known in the field prior to the filing date of the opposed application. The subjective "looks more like" standard proposed by HGS has no support in the application or the claims. It is an unworkably vague idea and it causes the scope of the claims to change over time, as more VEGF/PDGF family members are discovered.

11.15 As I explained above, this discussion of fragment, analogue, and derivative is only one example of why the HGS approach is unworkable, and why the claims encompass VEGF, PDGFa, PDGFb, and/or other subject matter known at the time of filing of the opposed application. I have reviewed Dr. Roger's declarations and agree with his analysis of other claims.

LACK OF CLARITY

A. Administration of a polypeptide according to claims 51 and 54.

12.1 The OPR1 declaration explained that claims 51 and 54 and claims dependent therefrom are confusing in that they recite administration of a polypeptide, but apparently would be met by treatment that does not involve administration of any polypeptide whatsoever. (OPR1 6.8.2) Dr. Mattick confirms that these claims are ambiguous by reading them to permit the limitation "administration . . . of the polypeptide" without administering any polypeptide. (AJM1 at 4.109 - 4.112.)

B. Indefiniteness of "fragment, analog, or derivative" claims.

12.2 The evidence in answer includes interpretations of "fragment, analog, or derivative" language that is intended to save the claims from encompassing the

prior art. As I have explained in Section 11 above, however, if such claim interpretations are adopted substantial issues of vagueness would ensue. Even if the standard proposed by HGS were , as new genes are discovered.

12.3 In the declaration of Dr. Gamble the term "fragment, analog, or derivative" is interpreted as follows:

> "Reference is made on page 9, line 14 to page 10, line 5 of the specification to the meaning of the terms "fragment", "derivative" and "analog". When I read these passages I understood HGS to be saying that a fragment, derivative or analogue is a polypeptide that retains essentially the same biological function or activity as VEGF-2." (AJG1 7.7).

12.4 I agree that there is some support at page 9 of the opposed application for the interpretation offered by Dr Gamble. Claim 56, however, is directed to a fragment, analogue, or derivative having an inhibitory activity. Dr. Mattick states that he understands other portions of the application as suggesting that VEGF2 fragments can have VEGF2 inhibitory activity. (See AJM1 4.23.) These claim interpretations are irreconcilable.

12.5 Dr. Gamble offers additional guidance regarding the definition of fragment, analogue, or derivative:

> "While I acknowledge this basic requirement I am conscious of the fact that before something can be an analogue, fragment or a derivative of a protein it needs to share sufficient identity with that protein to make it resemble that protein or at least part thereof. In my opinion both of these requirements must be satisfied before a sequence of amino acids can truly be called an analogue, fragment or a derivative of VEGF-2". (AJG1 at 7.7)

12.6 As I have explained above, neither conventional scientific usage nor the opposed application clarifies in any meaningful way what "sufficient

identity....to make it resemble" means. Even if the concept were understandable, I cannot see where the boundaries lie.

C. Indefiniteness of "polypeptide binds an antibody which binds to VEGF-2"

12.7 The term "polypeptide binds an antibody which binds to VEGF-2" (or some close variation thereof) is recited, or included by dependency, in at least claims 16-22 and 40-50 of the opposed application.

12.8 As shown by the following exemplary excerpts, the HGS evidence exhorts the Patent Office to believe that antibody cross-reactivity is too unpredictable to draw any conclusions from looking at protein sequences.

Dr Gamble at 7.21:

> "Associate Professor Rogers appears to suggest (see, for example paragraph 2.7.16) that antibodies that bind to regions of VEGF-2 that are conserved with other PDGF/VEGF family members might be cross-reactive. Associate Professor Rogers refers to a number of prior art disclosures of anti-VEGF or anti-PDGF antibodies. Simply because two sequences share some homology does not necessarily imply that any antibody produced against one molecule would necessarily be cross-reactive against the other. In my opinion no conclusion can be made as to whether sequences sharing some homology will generate antibodies that are cross reactive".

Dr Mattick at 4.33:

> "The fact that there is some sequence homology between VEGF-2 and VEGF and other proteins does not mean that there is a high probability that antibodies to VEGF-2 will cross react with VEGF or those other proteins. Antibodies generally have exquisite specificity and will only cross react with closely related proteins. I do not believe that any conclusion can be

drawn about cross-reactive antibodies at a theoretical or practical level".

12.9 If the premise of HGS's experts is accepted, then it is my opinion that all of the relevant claims which try to define subject matter via an antibody binding limitation are indefinite. HGS's position appears to be to require the physical screening of a relevant polypeptide with every antibody that could be generated against VEGF-2, in order to determine whether the polypeptide falls within a claim, a clearly impossible task. In addition, the boundaries of the claims are obscured by the fact that the cut-off level of binding is unspecified.

12.10 In criticising the Alitalo declaration, HGS's declarants appear to be of the opinion that the results of antibody binding experiments can be manipulated to achieve any result. For instance, manipulations to parameters such as antibody chosen (because antibodies have different binding affinities); selection of polyclonal versus monoclonal antibodies; the amount of antibodies used; and the lack of established controls, and I refer to ANH1 at 5.7. in this regard. If this is the case, then surely these claims that define a genus of polypeptides by whether they bind an antibody that binds VEGF2 are unclear. Essentially, HGS submits that antibody binding to a VEGF2 polypeptide can be manipulated to achieve a desired result, provided a number of parameters are carefully defined. However, no such parameters are defined in the patent application let alone in the claims at issue. In fact, this entire aspect of VEGF2 antibody binding is theoretical in the opposed application, since no antibodies are taught. Consequently, if antibody binding is subject to all of the variables and manipulations identified by HGS, then the scope of the claims are not clear.

D. Indefiniteness of "VEGF2 activity."

12.11 The OPR1 declaration explained that "VEGF2 activity" and related terms were indefinite. (See OPR1 at 6.5-6.5.1, 2.3-2.3.5, and 4.6-4.8.) The opposed application contains no explicit definition of VEGF2 activity, rather, it merely

suggests a number of *in vivo* or *in vitro* uses for VEGF2, which are all unsupported by evidence.

12.12 The declarations of HGS's expert witnesses cast further uncertainty on what is meant by "VEGF2 activity" - these declarations are all ambiguous about whether "VEGF2 activity" defines a single or multiple parameter in combination, or multiple parameters in the alternative:

12.12.1 In AJG1 (at 7-8) Dr. Gamble declares that she understands biological function or activity "to include at least *in vivo* and/or *in vitro* activity", thereby implying that she thinks all uses outlined in the patent application (e.g., culturing vascular endothelial cells, providing cancer therapy, promoting bone or periodontium or ligament growth, etc.) is VEGF2 activity. However, it remains ambiguous whether these functions/uses on their own represent VEGF2 activity or whether, when considered in their entirety, they comprise the definition of VEGF2 activity.

12.12.2 Elsewhere, Dr. Gamble suggests that a single biological function represents "VEGF2 activity." In her comments of paragraphs 7.9 and 7.10, and paragraphs 7.15-7.18, she seems to suggest that testing for angiogenic activity alone is a sufficient test for VEGF2 activity.

12.12.3 However, Dr Gamble is not consistent on this matter, in that she also suggests that a single biological function is insufficient for "VEGF2 activity." For example, in AJG1 7.11, Dr. Gamble indicates that a polypeptide promoting endothelial cell growth is a means for discriminating between a polypeptide having VEGF2 activity from a PDGFa or PDGFb polypeptide, which in her opinion does not promote endothelial cell growth. In this instance, she seems to be of the opinion that all VEGF2 polypeptides have at least endothelial cell growth activity since

it is on this basis that they are distinguished from PDGF polypeptides. However, such endothelial growth activity must, I assume, be in addition to the "angiogenic" activity she says she could have easily screened for (in AJG1 7.9-7.10 and 7.15-7.18), since Dr. Gamble is clearly of the opinion that PDGF polypeptides also have angiogenic activity, and I refer to Litwin, Gamble, and Vadas, Annexure GBC-10 of the HGS evidence, at page 105 (PDGF "has roles in wound healing and angiogenesis") in this regard.

12.12.4 Dr. Hayward indicates that VEGF2 activity means "one or more" of a list of about seven activities. (See ANH1 3.6) His list explicitly omits many other functions taught in the opposed application, such as growth of damaged bone, periodontium, or ligament tissue (page 17 of the opposed application). Therefore, it is unclear whether Dr. Hayward now classifies one or more of these other functions as VEGF2 activities. (At paragraph 4.4, Dr. Hayward makes generic reference to all of the activities recited at pages 4 and 16-18 of the application.) Dr. Hayward also indicates that whether the specification teaches a unique defining activity for VEGF2 is irrelevant. (ANH1 at 4.3.)

12.13 Therefore, when outlining the alleged simplicity of understanding and screening for VEGF2 activity, HGS's expert witnesses merely create confusion. For example, if VEGF2 means "angiogenic activity", why does the application teach that VEGF2 did so many other things. Also, how does "VEGF2 activity" distinguish the angiogenic PDGF and VEGF polypeptides of the prior art? Further, if "VEGF2 activity" includes a combination of "endothelial growth activity" and "angiogenesis activity" (per Dr. Gamble, to exclude PDGF from the claims), then why does Dr. Gamble suggest elsewhere in her declaration that the only testing she would have needed to do was testing for "angiogenic activity"? On this basis, how does this definition of "VEGF2 activity" exclude prior art VEGF polypeptides, which promote

endothelial cell growth and angiogenesis? Also, if the combination of "angiogenic activity" and "endothelial growth activity" are the two functions that are critical for defining "VEGF2 activity", why does the application identify so many other functions. Similarly, it is also unclear to me why the HGS declarants broadly say that VEGF2 activity is "*in vitro* and/or *in vivo*" activity? Furthermore, with such a multitude of other functions mentioned in the application why, except perhaps for hindsight, were angiogenic activity and/or endothelial cell growth activity selected by the HGS declarants as the two important activities? If a protein is capable of inducing growth of damaged bone, periodontium, or ligament tissue as stated in the application at page 17, does that protein have VEGF2 activity? Does the answer depend on whether it also promotes angiogenesis and endothelial cell growth? On this basis, I find that the declarations of HGS's experts do no more than confuse further the meaning of "VEGF2 activity."

12.14 The ambiguities regarding activity are perhaps best illustrated in the context of representative HGS claims. For example, claim 28 attempts to encompass "an active fragment, analog or derivative" of the VEGF2 polypeptide of Figure 1 of the application. Claim 34 attempts to encompass a polypeptide "having VEGF-2 biological activity". It is unclear from the patent application or from the HGS declarations whether any or all of the following polypeptides would satisfy these "activity" claim limitations:

(a) A polypeptide that stimulates endothelial cell growth and has no other measurable effects;

(b) A polypeptide that stimulates angiogenesis and has no other measurable effects;

(c) A polypeptide that stimulates endothelial cell growth and angiogenesis but has not other effects;

(d) A polypeptide that induces the growth of bone and ligament tissue but has no effect on endothelial cell growth or angiogenic activity; and

(e) A polypeptide that induces the formation of antibodies that can bind to VEGF2, but inhibits endothelial cell growth and inhibits angiogenesis.

Because one cannot determine what characteristics are necessary and sufficient to satisfy the activity limitations of the claims, one cannot know for certain whether a polypeptide falls within the claims based on its activities. I find the claims ambiguous in this regard.

AND I MAKE this solemn declaration by virtue of the Statutory Declarations Act 1959, and subject to the penalties provided by that Act for the making of false statements in statutory declarations, conscientiously believing the statements contained in this declaration to be true in every particular.

DECLARED at Adelaide

This 12th day of December, 2001

Francis John Ballard

Before me:

(Signature of Witness)

Lynette C. Kirkwood (Pharmacist)

APPENDIX I

EXEMPLARY PORTIONS OF HGS EVIDENCE DEVOTED TO EXPERIMENTATION TO TRY TO COMPLETE THE VEGF2 INVENTION

Further experimentation suggested by Dr. Mattick in order to understand the VEGF2 invention or how to make it work:

AJM1 3.15	Computer analysis of sequence for signal peptide.
AJM1 3.16-19	Expression of protein from DNA
AJM1 3.18	Overcoming obstacle of realizing that protein doesn't express because signal sequence is missing or faulty.
AJM1 3.33	Experimentation to express a biologically active VEGF2
AJM1 3.34	Experimentation to obtain VEGF2 polynucleotide sequences.
AJM1 4.3-4.13	Experimentation to express VEGF2 notwithstanding "the fact that the signal sequence information was incomplete" in the opposed application.
AJM1 4.15-4.16	Confirming biological activity, suggestion of collaboration
AJM1 4.64-4.68	Experimentation to produce fragments analogues and derivatives, and identification of such molecules
AJM1 4.77	Expression of incomplete sequence
AJM1 4.82-4.83	Production of antibodies and determination of VEGF2 activity

Further experimentation suggested by Dr. Gamble in order to understand the VEGF2 invention or how to make it work:

AJG1 5.14-5.19	Assaying for angiogenic properties
AJG1 7.9-7.10	Testing for *in vivo* or *in vitro* activity
AJG1 7.11	Distinguishing between growth factors
AJG1 7.20	Antibody production
AJG1 7.35	Experimentation to produce fragments analogues and derivatives

Further experimentation suggested by Dr. Hayward in order to understand the VEGF2 invention or how to make it work:

ANH1 3.11-3.12	Designing suitable hybridization conditions
ANH1 3.19-3.21,4.20	Use of heterologous signal sequence
ANH1 3.25	5' end cloning
ANH1 3.27	Testing for a biological activity
ANH1 3.29	Testing VEGF2 in proliferation, angiogenesis and wound healing assays
ANH1 3.34	Testing of receptor binding
ANH1 4.4	Activity assays
ANH1 4.26-4.27	Redesigning Example 2 in the application in order to attempt to achieve the results that were reported

Further experimentation suggested by Dr. Rapoport in order to understand the VEGF2 invention or how to make it work: (essentially entire declaration, devoted to identifying signal peptide defect in patent application, and then trying to overcome it.)

Further experimentation suggested by Dr. Aaronson in order to understand the VEGF2 invention or how to make it work:

ASA1 at 16	Engineering a heterologous signal sequence

Further experimentation suggested by Dr. Power in order to understand the VEGF2 invention or how to make it work: (Entire Declaration devoted to signal peptide experiments which are not based on the applications teachings.)

APPENDIX II

EXEMPLARY PORTIONS OF HGS EVIDENCE DEVOTED TO CATALOGUING PREDICTIONS IN THE PATENT APPLICATION

Cataloging by Dr. Mattick of statements, unsupported predictions, and other unsupported excerpts of the HGS application:

AJM1 3.25, 3.30-3.31 (Alleged uses of VEGF2 - no supporting data)

AJM1 3.32 and JSM-4 Table 1 (essentially a table of contents for application.)

AJM1 4.3 and 4.5-4.11 (overcoming signal sequence issue)

AJM1 4.18-4.24 (biological properties of VEGF2 and theoretical uses)

AJM1 4.30 and 4.39 (hybridization conditions and control thereof)

AJM1 4.67 (testing for activity),

AJM1 4.70 and 4.73 (gene therapy and treatments)

AJM1 4.77 (heterologous signal sequence usage)

AJM1 4.82-4.83 (antibody production)

AJM1 4.108 (antagonists)

Cataloging by Dr. Gamble of predictions and other unsupported excerpts of the HGS application:

AJG1 6.5 (prediction of processing)

AJG1 6.6 (expression systems)

AJG1 6.7 (activity assays)

AJG1 6.8 - 6.8.11 (list like Mattick)

AJG1 7.11 (assays for fragments, etc)

AJG1 7.15-7.18 (angiogenic assays)

AJG1 7.20 (generation of antibodies)

AJG1 7.24 (prediction of processing)

AJG1 7.35 (generation of fragments)

Cataloging by Dr. Hayward of predictions and other unsupported excerpts of the HGS application:

ANH1 3.6 (activities fo VEGF2 and/or fragments, etc.)

ANH1 3.11 (hybridization conditions)

ANH1 3.15 (expectation of secretion)

ANH1 3.19-3.21 (use of heterologous signal sequence)

ANH1 3.22 (processing)

ANH1 3.27-3.30 (activities and uses of VEGF2)

ANH1 3.34 &3.35 (binding of receptors)

ANH1 3.37 (uses of fragments and antibodies)

ANH1 4.4 (assays and activities)

Cataloging by Dr. Rapoport of predictions and other unsupported excerpts of the HGS application:

ATR1 at 11 (prediction of processing)

ATR1 at 12 (heterologous signal sequence)

ATR1 at 18 (prediction of a secreted growth factor)

Cataloging by Dr. Aaronson of predictions and other unsupported excerpts of the HGS application:

ASA1 at 5 (prediction of secretion)

ASA1 at 6 (proteolytic processing)

ASA1 at 16 (heterologous signal sequence)

AUSTRALIA

Patents Act 1990

IN THE MATTER OF Australian Patent Application Serial No. 696764 by Human Genome Sciences, Inc.

-and-

IN THE MATTER OF Opposition thereto by Ludwig Institute for Cancer Research

THIS IS Exhibit FJB-1

referred to in the Statutory Declaration

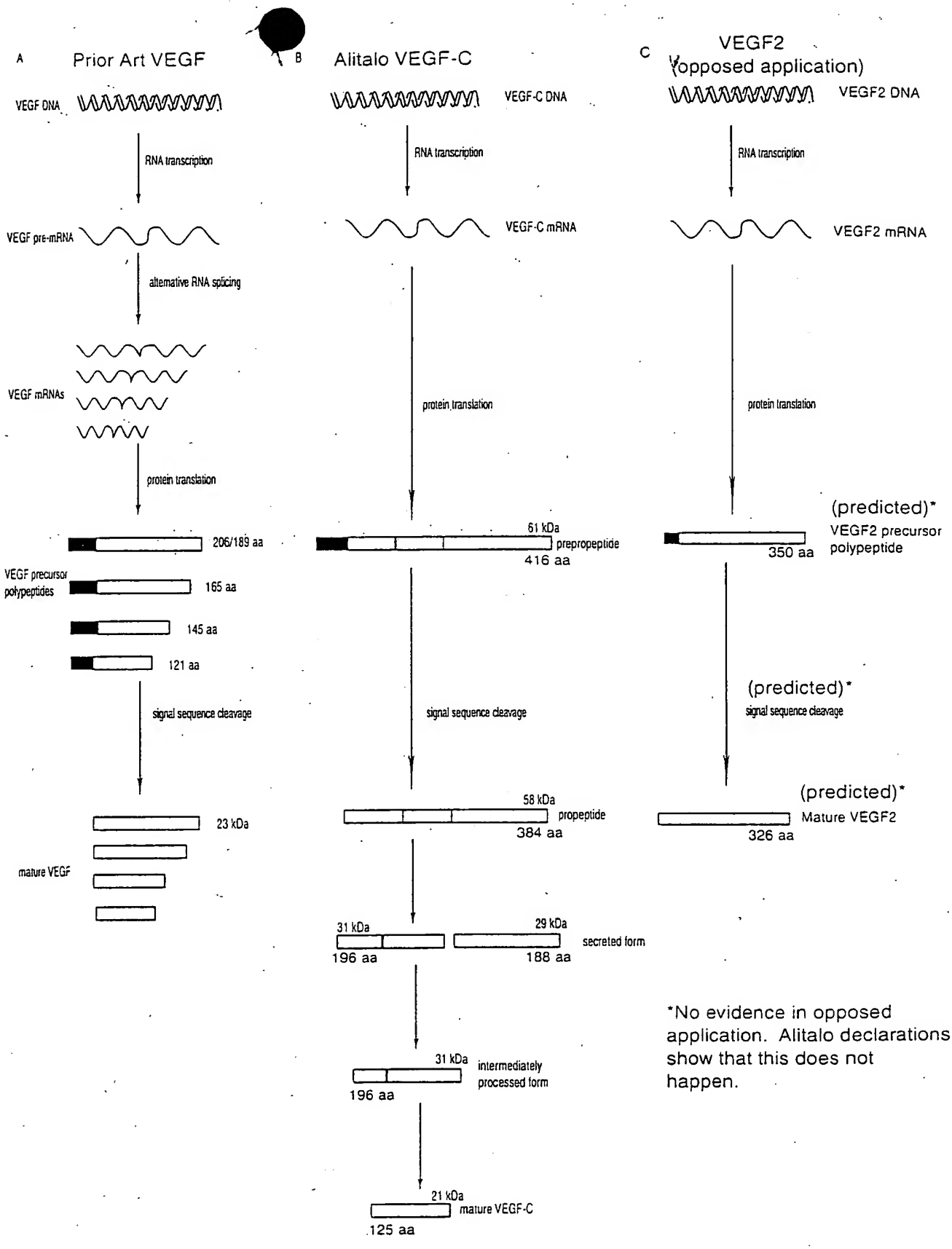
of Francis John Ballard

made before me

DATED this 12 Day of December, 2001

(Signature of Witness)

Lynette C. Kirkwood (Pharmacist)



*No evidence in opposed application. Alitalo declarations show that this does not happen.